Kaohsiung Journal of Medical Sciences (2016) 32, 255–260

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Comparison of vonoprazan and proton pump inhibitors for eradication of *Helicobacter pylori*

Satoshi Shinozaki [a], Hiroaki Nomoto [b], Yoshie Kondo [b], Hirotsugu Sakamoto [c], Yoshikazu Hayashi [c], Hironori Yamamoto [c], Alan Kawarai Lefor [d], Hiroyuki Osawa [c,*]

[a] *Shinozaki Medical Clinic, Utsunomiya, Japan*
[b] *Department of Gastroenterology, Haga Red Cross Hospital, Moka, Japan*
[c] *Division of Gastroenterology, Department of Medicine, Jichi Medical University, Shimotsuke, Japan*
[d] *Department of Surgery, Jichi Medical University, Shimotsuke, Japan*

Received 11 January 2016; accepted 18 April 2016
Available online 21 May 2016

KEYWORDS
Antibiotics;
Gastric acid;
Helicobacter pylori;
Proton pump inhibitors;
Treatment outcome

Abstract Alternative eradication therapies for *Helicobacter pylori* infection are needed because of an increasing failure rate over the past decade. The aim of this study was to determine if vonoprazan, a new potassium-competitive acid blocker, showed superiority to existing proton pump inhibitors for primary eradication of *H. pylori* in routine clinical practice. Data for 573 patients who underwent primary *H. pylori* eradication therapy were retrospectively reviewed. Regimens included clarithromycin 200 mg, amoxicillin 750 mg, and an acid-suppressing drug [lansoprazole 30 mg (LAC), rabeprazole 10 mg (RAC), esomeprazole 20 mg (EAC), or vonoprazan 20 mg (VAC)] twice daily for 1 week. Eradication was successful in 73% (419/573) of patients using intention-to-treat (ITT) analysis and 76% (419/549) of patients in per-protocol (PP) analysis. The VAC group had a significantly superior eradication rate compared with the LAC and RAC groups in ITT (VAC 83%, LAC 66% and RAC 67%, $p < 0.01$) and PP analysis (VAC 85%, LAC 69% and RAC 70%, $p < 0.01$), and had a similarly high eradication rate to the EAC group (83% in ITT and 87% in PP). Although the eradication rate in the VAC and EAC groups was not significantly higher than in the LAC and RAC groups in patients with mild gastric atrophy with both ITT and PP analyses, it was significantly higher in patients with severe gastric atrophy ($p < 0.01$). The VAC group had a significantly higher *H. pylori* eradication rate

Conflicts of interest: Author S.S. has received honoraria from Takeda and Eisai Pharmaceuticals. Author Y.K. received honoraria from AstraZeneca Pharmaceuticals. Author H.S. received a research grant from Takeda. Author Y.H. has received honoraria from AstraZeneca, Eisai and Daiichi Sankyo Pharmaceuticals. Author H.Y. has received research grants and honoraria from Takeda, Otsuka, AstraZeneca, Eisai and Daiichi Sankyo Pharmaceuticals. Author H.O. received research grants and honoraria from Takeda, AstraZeneca and Daiichi Sankyo Pharmaceuticals. The funding source had no role in the design, practice or analysis of this study. Other authors have no conflicts of interest to report.

* Corresponding author. Division of Gastroenterology, Department of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan.
E-mail address: osawa@jichi.ac.jp (H. Osawa).

http://dx.doi.org/10.1016/j.kjms.2016.04.009

than the LAC and RAC groups, and a > 80% eradication rate regardless of the degree of atrophy.

Introduction

Curative therapy for *Helicobacter pylori* infection has become a major interest for gastroenterologists over the past 2 decades, because eradication of *H. pylori* decreases the incidence of future gastric cancer as well as gastroduodenal ulcers [1]. In Japan, standard triple therapy has been approved for the treatment of *H. pylori*-infected peptic ulcer by the national health insurance system since 2000, and consists of using a proton pump inhibitor (PPI) with amoxicillin and clarithromycin twice daily for 1 week. At that time, three kinds of PPIs including omeprazole, lansoprazole, and rabeprazole were available in Japan. In 2013, the Japanese health insurance system began reimbursement for primary *H. pylori* eradication therapy in patients with *H. pylori* gastritis diagnosed by esophagogastroduodenoscopy (EGD). Since that time, the number of patients receiving eradication therapy has been increasing.

However, the primary *H. pylori* eradication rate has been decreasing to an unacceptable level over the past decade [2,3]. The recent subsequent increase in bacterial resistance to clarithromycin in Japan led to a decline in successful eradication using first-line therapy [4]. Therefore, a novel strategy for primary *H. pylori* eradication has been sought. Esomeprazole (an S-isomer of omeprazole), a second generation PPI, suppresses gastric acid secretion more strongly, resulting in improved susceptibility to antibiotics by *H. pylori*. In 2011, this drug was released in Japan and made available for *H. pylori* eradication therapy. A meta-analysis showed the superiority of esomeprazole in the primary eradication of *H. pylori* compared with other PPIs [5]. In 2015, vonoprazan, a member of a new class of potassium-competitive acid blockers (P-CAB), was released and approved for use in *H. pylori* eradication in Japan. Although PPIs decrease gastric acid secretion by inhibiting H^+, K^+-ATPase in parietal cells, P-CABs do this by directly inhibiting H^+-K^+ exchange on the gastric luminal surface. Vonoprazan suppresses gastric acid secretion through this alternative mechanism [6].

Recently, the superiority of vonoprazan over lansoprazole for primary *H. pylori* eradication therapy was reported, with an eradication rate of 93% for vonoprazan and 76% with lansoprazole ($p < 0.01$) [7]. However, few reports are available regarding the rate of eradication employing both PPIs and P-CAB. The aim of this study was to determine if this new P-CAB shows superiority to existing PPIs for the primary eradication of *H. pylori* in routine clinical practice.

Patients and methods

Study population

We retrospectively reviewed the medical records of 573 patients who underwent standard primary *H. pylori* eradication therapy at Haga Red Cross Hospital (Moka, Japan) and Shinozaki Medical Clinic (Utsunomiya, Japan) between April 2013 and July 2015. Abstracted data include age, sex, *H. pylori* presence test used, prior PPI or vonoprazan use, type of PPI or vonoprazan used for eradication, EGD findings, and side effects. All patients underwent EGD because the Japanese national health insurance system requires the diagnosis of *H. pylori* gastritis by EGD prior to performing an *H. pylori* presence test. Positive *H. pylori* status was established by a rapid urease test, histology, stool antigen test, serology (serum IgG), or ^{13}C-urea breath test (UBT). The degree of atrophy was endoscopically evaluated based on the Kimura—Takemoto classification, in which closed and open types correspond to mild and severe atrophy, respectively [8]. The Institutional Review Board approved this study.

Primary H. pylori eradication

Standard triple therapy in Japan includes clarithromycin 200 mg, amoxicillin 750 mg, and an acid suppression drug [lansoprazole 30 mg (LAC), rabeprazole 10 mg (RAC), esomeprazole 20 mg (EAC), or vonoprazan 20 mg (VAC)] twice daily for 1 week. The choice of acid-suppressing drug was made by the physician in charge. Data regarding vonoprazan have been gathered since its release in Japan in February 2015. Based on previous favorable eradication data using vonoprazan [7], its use has predominated since early 2015. For the evaluation of successful eradication, a UBT or stool antigen test was used at least 8 weeks after the eradication period. The cut-off value for the UBT was 2.5‰. Before the UBT, PPI or vonoprazan intake was suspended for at least 2 weeks for a patient taking a PPI or vonoprazan. Successful primary *H. pylori* eradication therapy was determined by a negative UBT or stool antigen test. The stool antigen test was mostly used for patients who had undergone distal gastrectomy. The success rate of eradication was assessed by intention-to-treat (ITT) and per-protocol (PP) analyses. Exclusion criteria for PP analysis included: (1) patients who showed poor compliance (< 50%); and (2) patients who did not return to the clinic to receive a UBT or stool antigen test for evaluating the results of eradication therapy. All patients treated, but not included in the PP analysis, were considered to have failed eradication.

Statistical analysis

Statistical analysis was performed using BellCurve for Excel 2015 software (Social Survey Research Information Co., Ltd. Tokyo, Japan). Categorical data were assessed using Fisher's exact test. Differences in data with $p < 0.05$ are considered statistically significant.

Table 1 Demographic data and endoscopic findings.

Number	Total	LAC	RAC	EAC	VAC
	573	198	138	120	117
Age (y), mean ± SD	63.5 ± 12.1	62.7 ± 12.4	63.7 ± 11.0	65.1 ± 10.9	63.0 ± 13.7
Gender, male	286 (50)	88 (44)	70 (51)	74 (62)	54 (46)
Prior PPI or vonoprazan use	192 (34)	68 (34)	37 (27)	43 (36)	44 (38)
Endoscopic findings					
Reflux esophagitis, LA grade A/B/C/D	18/6/1/0	5/1/0/0	8/2/0/0	2/2/0/0	3/1/1/0
Gastric ulcer/scar	68 (12)	21 (11)	13 (9)	24 (20)	10 (9)
Duodenal ulcer/scar	54 (9)	18 (9)	12 (9)	13 (11)	11 (9)
Gastric hyperplastic polyp	63 (11)	22 (11)	12 (9)	17 (14)	12 (10)
Atrophic change[a]					
Mild	102 (18)	44 (23)	24 (18)	13 (11)	21 (18)
Severe	460 (82)	149 (77)	109 (82)	107 (89)	95 (82)
Status post distal gastrectomy	11 (2)	5 (3)	5 (4)	0 (0)	1 (1)
Side effects	38 (7)	21 (11)	8 (6)	3 (3)	6 (5)
Per-protocol	549 (96)	189 (95)	132 (96)	114 (95)	114 (97)
Confirming successful eradication using UBT/stool antigen test	533/16	183/6	127/5	114/0	109/5

Data are presented as *n* (%) unless otherwise indicated.
EAC = esomeprazole-based regimen; LA = Los Angeles; LAC = lansoprazole-based regimen; PPI = proton pump inhibitor; RAC = rabeprazole-based regimen; SD = standard deviation; VAC = vonoprazan-based regimen; UBT = ^{13}C-urea breath test.
[a] Patients status post distal gastrectomy were excluded.

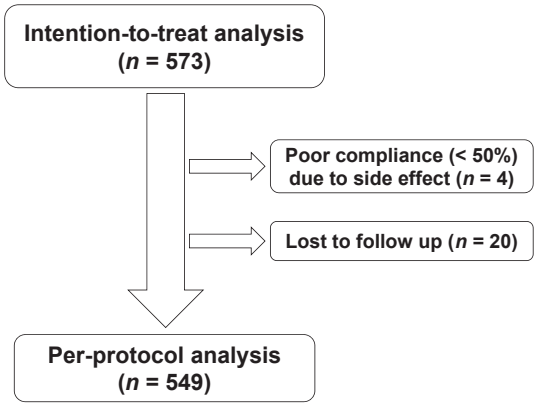

Figure 1. Study flowchart.

Table 2 Comparison of vonoprazan and proton pump inhibitors for eradication of *Helicobacter pylori*.

	Total	LAC	RAC	EAC	VAC
ITT analysis (%)	73	66	67	83*	83*
(95% CI)	(69–77)	(59–72)	(58–74)	(75–89)	(75–89)
n	419/573	131/198	92/138	99/120	97/117
PP analysis (%)	76	69	70	87*	85*
(95% CI)	(73–80)	(62–76)	(61–77)	(79–93)	(77–91)
n	419/549	131/189	92/132	99/114	97/114

* $p < 0.01$ compared with LAC or RAC groups.
CI = confidence interval; EAC = esomeprazole-based regimen; ITT = intention-to-treat analysis; LAC = lansoprazole-based regimen; PP = per-protocol analysis; RAC = rabeprazole-based regimen; VAC = vonoprazan-based regimen.

Results

Clinical characteristics

Baseline characteristics and endoscopic data of the patients in each group are shown in Table 1. The mean age among all patients was 64 years. More than 80% of patients had severe gastric atrophy on endoscopy. The proportion of patients with PP treatment was comparatively high (96%; Figure 1). Side effects were observed in 7% of patients, including bitter taste, diarrhea, and skin rash.

Success rate of primary H. pylori eradication

The overall rate of successful eradication was 73% (419/573) in ITT analysis and 76% (419/549) in PP analysis (Table 2). The VAC group had a significantly superior eradication rate compared with the LAC and RAC groups, and had a similarly high eradication rate to the EAC group.

A lower eradication rate in patients with severe atrophy has been reported compared with patients with mild atrophy [9]. Based on the degree of gastric atrophy, eradication rates among the four patient groups were compared after excluding 11 patients who were status post distal gastrectomy. The VAC group had the highest rate of eradication for patients with mild gastric atrophy among the four groups, although not a significant difference (Figure 2A). In patients with severe gastric atrophy, both the VAC and EAC groups had a significantly higher eradication rate than the LAC and RAC groups ($p < 0.01$; Figure 2B). Only vonoprazan had a > 80% eradication rate in patients with both mild and severe gastric atrophy.

Discussion

The eradication rate of *H. pylori* using VAC was significantly higher than with LAC and RAC, in both ITT and PP analyses, and showed a similar rate to EAC. In patients with severe atrophy in this study, LAC and RAC groups had a significantly

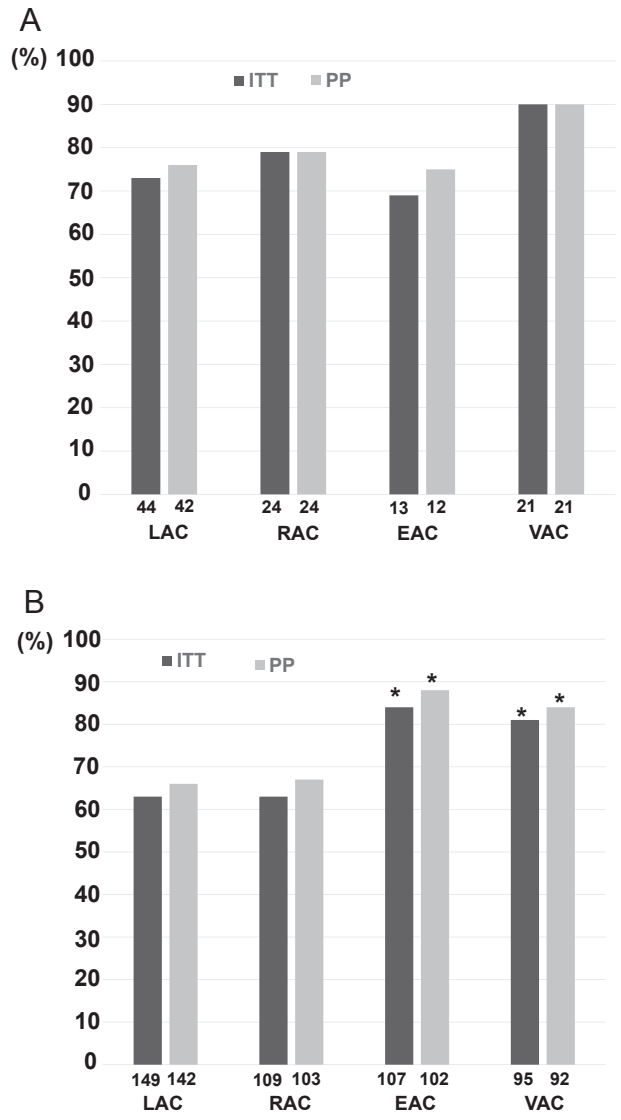

Figure 2. Eradication rate in patients with (A) mild gastric atrophy and (B) severe gastric atrophy. Figures for each regimen show the number of patients. * $p < 0.01$ compared with LAC and RAC groups. EAC = esomeprazole-based regimen; ITT = intention-to-treat analysis; LAC = lansoprazole-based regimen; PP = per-protocol analysis; RAC = rabeprazole-based regimen; VAC = vonoprazan-based regimen.

lower eradication rate compared with EAC and VAC groups, but not in patients with mild atrophy. Furthermore, only VAC had a > 80% eradication rate regardless of the degree of atrophy. The strong acid inhibition by vonoprazan and esomeprazole may have contributed to the observed increase in the rate of successful primary *H. pylori* eradication.

In this study, the VAC group had a favorable eradication rate in spite of increasing antibiotic resistance in Japan over the past decade [10]. The clinical effect of acid-suppressing drugs was evaluated by the duration and degree of acid inhibition [11]. Sugimoto et al. [12] reported that sustained gastric pH > 4.0 was important for successful *H. pylori* eradication. Vonoprazan acts by inhibition of the H^+, K^+-ATPase pathway, with competitive and sustained blockade, and provides rapid elevation of intragastric pH [6]. The Japanese randomized prospective study reported that a vonoprazan-based regimen was superior to the same lansoprazole-based regimen (93% vs. 76%, $p < 0.001$) [7]. The difference (17%) in eradication rates in that study is similar to the difference observed in the present study (17%). Strong acid suppression through inhibition of the H^+, K^+-ATPase pathway may at least partially explain this difference. Consistent with results reported in a meta-analysis [5], the EAC group also had a similar superiority to the LAC and RAC groups in this study. However, VAC did not show superiority to EAC therapy. In a healthy volunteer study using 24-hour pH monitoring, the acid-inhibitory effect of vonoprazan was superior to that of esomeprazole [13]. Although the study used once daily doses of 20 mg vonoprazan and 20 mg esomeprazole, twice daily 20 mg esomeprazole is used in *H. pylori* eradication therapy and may provide adequate acid suppression for *H. pylori* eradication. Kagami et al. [14] recently reported that a difference in the median pH ≥ 4 holding time ratio between vonoprazan 20 mg twice daily and esomeprazole 20 mg twice daily was only 9%. Therefore, the small difference in acid-inhibitory effect in the twice daily models comparing vonoprazan and esomeprazole may explain the similar success rate of eradication.

The variation in acid inhibition by PPI is associated with CYP2C19 genotypes, but CYP3A4 is mainly responsible for the metabolism of vonoprazan. Thus, vonoprazan maintains high pH levels in gastric glands even in CYP2C19 rapid metabolizers [15]. In addition, the inhibitory effect of vonoprazan (pKa 9.4) on gastric acid secretion is largely unaffected by ambient pH, as it accumulates in the parietal cells under both acidic and neutral conditions [16,17]. Antibiotics are more stable in a less-acidic environment and induce higher antibiotic sensitivity in bacteria, leading to high efficacy of eradication [18,19]. It has also been reported that twice-daily dosing of esomeprazole also inhibits acid secretion, even in CYP2C19 rapid metabolizers, compared with twice-daily rabeprazole or lansoprazole [20]. Esomeprazole leads to a steadily high pH sufficient to eradicate *H. pylori*, but the use of rabeprazole or lansoprazole leads to a pH that is less stable. These data suggest that some patients treated with rabeprazole or lansoprazole may have relatively low intragastric pH during the eradication period.

Gastric atrophy is a risk factor for gastric cancer that increases with the progression of atrophy. Therefore, the success rate of *H. pylori* eradication is important in patients with severe gastric atrophy. Recently, a lower eradication rate in patients with severe atrophy compared with those with mild atrophy has been reported [9]. This suggests that severe atrophy is a risk for eradication failure. In patients with severe atrophy in this study, LAC and RAC groups had a significantly lower eradication rate compared with EAC and VAC groups, but not in patients with mild atrophy. Data from the EAC/VAC groups indicate that high gastric pH may be necessary to eradicate *H. pylori* in patients with severe atrophy. The LAC and RAC groups may have low pH, making it impossible to eradicate *H. pylori* in the presence of severe atrophic changes. The precise

explanation for these observations remains unknown, as reported recently [9]. We suggest four possible explanations for these observations: (1) severe atrophy prolongs gastric emptying that may cause deactivation of enteric-coated tablets [21,22]. Unlike PPIs, vonoprazan is not supplied as enteric-coated tablets; (2) unlike lansoprazole and rabeprazole, esomeprazole can maintain gastric pH $>$ 5 even in patients who have the extensive metabolizer of CYP2C19 genotype [20]; (3) there may be instability of lansoprazole or rabeprazole in the secretory vesicles of parietal cells or the presence of fewer parietal cells in patients with severe atrophic changes; and (4) because serum anti-*H. pylori* titers reflecting bacterial proliferation are inversely correlated to the extent of intestinal metaplasia, *H. pylori* proliferation may be decreased in patients with severe gastric atrophy resulting in low susceptibility to antibiotics [23].

Some advantages of this study were that the treatment regimens were homogeneous, and complete EGD findings were available for all patients as well as extensive follow up. All patients were treated with the same dose of clarithromycin and amoxicillin for the same duration. The availability of endoscopic findings for all patients enabled analysis of the relationship between successful eradication and the degree of atrophy. However, there are some acknowledged limitations to this study. ITT and PP analysis were performed in a retrospective, nonrandomized, non-control study. Antibiotic resistance and CYP2C19 expression were not evaluated. The time frame for the eradication period in the VAC group was different from patients receiving existing PPIs because vonoprazan was released in February 2015 in Japan. Three regimens (LAC, RAC, and EAC) were used in 2013—2015 and one regimen (VAC) was begun in 2015. Because clarithromycin resistance has been increasing recently [3,24], there may be a higher rate of resistance in 2015 than in 2013—2014. In this study, the VAC group may be at a disadvantage compared with patients receiving existing PPIs. These factors may limit the ability to generalize the conclusions of this study, and these retrospective data have to be carefully interpreted.

In conclusion, treatment with the VAC regimen had a significantly higher *H. pylori* eradication rate than the LAC and RAC regimens, and a similar eradication rate as the EAC regimen. Severe gastric atrophy makes *H. pylori* eradication difficult in patients treated with LAC and RAC regimens, however, the eradication rate is not affected by the degree of atrophy in patients receiving the VAC regimen. Future large prospective studies are necessary to confirm these conclusions.

References

[1] Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008;372:392—7.

[2] Gong EJ, Yun SC, Jung HY, Lim H, Choi KS, Ahn JY, et al. Meta-analysis of first-line triple therapy for helicobacter pylori eradication in Korea: is it time to change? J Korean Med Sci 2014;29:704—13.

[3] Kawai T, Takahashi S, Suzuki H, Sasaki H, Nagahara A, Asaoka D, et al. Changes in the first line *Helicobacter pylori* eradication rates using the triple therapy-a multicenter study in the Tokyo metropolitan area (Tokyo Helicobacter pylori study group). J Gastroenterol Hepatol 2014;29(Suppl. 4): 29—32.

[4] Rimbara E, Noguchi N, Tanabe M, Kawai T, Matsumoto Y, Sasatsu M. Susceptibilities to clarithromycin, amoxycillin and metronidazole of *Helicobacter pylori* isolates from the antrum and corpus in Tokyo, Japan, 1995—2001. Clin Microbiol Infect 2005;11:307—11.

[5] Wang X, Fang JY, Lu R, Sun DF. A meta-analysis: comparison of esomeprazole and other proton pump inhibitors in eradicating *Helicobacter pylori*. Digestion 2006;73:178—86.

[6] Hunt RH, Scarpignato C. Potassium-competitive acid blockers (P-CABs): are they finally ready for prime time in acid-related disease? Clin Transl Gastroenterol 2015;6:e119.

[7] Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. Gut 2016. http://dx.doi.org/10.1136/gutjnl-2015-311304.

[8] Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy 1969;1:87—97.

[9] Kalkan IH, Sapmaz F, Guliter S, Atasoy P. Severe gastritis decreases success rate of *Helicobacter pylori* eradication. Wien Klin Wochenschr 2015; Dec 4 [Epub ahead of print].

[10] Kobayashi I, Murakami K, Kato M, Kato S, Azuma T, Takahashi S, et al. Changing antimicrobial susceptibility epidemiology of *Helicobacter pylori* strains in Japan between 2002 and 2005. J Clin Microbiol 2007;45:4006—10.

[11] Bell NJ, Burget D, Howden CW, Wilkinson J, Hunt RH. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion 1992;51(Suppl. 1):59—67.

[12] Sugimoto M, Furuta T, Shirai N, Kodaira C, Nishino M, Ikuma M, et al. Evidence that the degree and duration of acid suppression are related to *Helicobacter pylori* eradication by triple therapy. Helicobacter 2007;12:317—23.

[13] Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42:719—30.

[14] Kagami T, Sahara S, Ichikawa H, Uotani T, Yamade M, Sugimoto M, et al. Potent acid inhibition by vonoprazan in comparison with esomeprazole, with reference to CYP2C19 genotype. Aliment Pharmacol Ther 2016;43:1048—59.

[15] Ashida K, Sakurai Y, Hori T, Kudou K, Nishimura A, Hiramatsu N, et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. Aliment Pharmacol Ther 2016;43:240—51.

[16] Matsukawa J, Hori Y, Nishida H, Kajino M, Inatomi N. A comparative study on the modes of action of TAK-438, a novel potassium-competitive acid blocker, and lansoprazole in primary cultured rabbit gastric glands. Biochem Pharmacol 2011; 81:1145—51.

[17] Hori Y, Matsukawa J, Takeuchi T, Nishida H, Kajino M, Inatomi N. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. J Pharmacol Exp Ther 2011;337: 797—804.

[18] Calvet X, Gomollon F. What is potent acid inhibition, and how can it be achieved? Drugs 2005;65(Suppl. 1):13—23.

[19] Sachs G, Scott DR, Wen Y. Gastric infection by *Helicobacter pylori*. Curr Gastroenterol Rep 2011;13:540—6.

[20] Sahara S, Sugimoto M, Uotani T, Ichikawa H, Yamade M, Iwaizumi M, et al. Twice-daily dosing of esomeprazole effectively inhibits acid secretion in CYP2C19 rapid metabolisers compared with twice-daily omeprazole, rabeprazole or lansoprazole. Aliment Pharmacol Ther 2013;38:1129—37.
[21] Kalkan C, Soykan I, Soydal C, Ozkan E, Kalkan E. Assessment of gastric emptying in patients with autoimmune gastritis. Dig Dis Sci 2016; Jan 2 [Epub ahead of print].
[22] Tucci A, Poli L, Biasco G, Paparo GF, Tosetti C, Fusaroli P, et al. *Helicobacter pylori* infection and gastric function in patients with fundic atrophic gastritis. Dig Dis Sci 2001;46:1573—83.
[23] Osawa H, Inoue F, Yoshida Y. Inverse relation of serum *Helicobacter pylori* antibody titres and extent of intestinal metaplasia. J Clin Pathol 1996;49:112—5.
[24] Liou JM, Chang CY, Chen MJ, Chen CC, Fang YJ, Lee JY, et al. The primary resistance of *Helicobacter pylori* in Taiwan after the national policy to restrict antibiotic consumption and its relation to virulence factors—a nationwide study. PLoS One 2015;10:e0124199.